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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--------------------------------------|-------------|----------------------|---------------------|------------------|
| 09/079,640 | 05/15/1998 | HENRY DANIELL | 922.6588P | 8567 |
| 22469 | 7590 | 11/17/2004 | EXAMINER | |
| SCHNADER HARRISON SEGAL & LEWIS, LLP | | | FOX, DAVID T | |
| 1600 MARKET STREET | | | | |
| SUITE 3600 | | | ART UNIT | |
| PHILADELPHIA, PA 19103 | | | PAPER NUMBER | |
| | | | 1638 | |

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | | |
|------------------------------|------------------------|--|---------------------|--|
| Office Action Summary | Application No. | | Applicant(s) | |
| | 09/079,640 | | DANIELL, HENRY | |
| | Examiner | | Art Unit | |
| | David T. Fox | | 1638 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 6/28/2004 & 9/7/2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-96,100-191,193-196,200-214 and 216-223 is/are pending in the application.
- 4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.
- 5) ☒ Claim(s) 4-84,86-96,107,168,169,172-176,189,194 and 195 is/are allowed.
- 6) ☒ Claim(s) 3,118,119,122,171,190,191,193,196,214 and 216-223 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Continuation of Disposition of Claims: Claims withdrawn from consideration are 1,85,100-106,108-117,120,121,123-167,170,177-188 and 200-213.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's request for RCE filed on 28 June 2004 has been entered. Applicant's amendments of 28 June 2004 were not in compliance with 37 CFR 1.121, as indicated by the paper mailed 09 July 2004. Applicant's arguments accompanying the amendment of 28 June 2004 were not reproduced in subsequent amendment submissions. Accordingly, Applicant's arguments of 28 June 2004 have been relied upon when preparing the instant Office action. Applicant's amendments of 07 September 2004 are in compliance with 37 CFR 1.121 and have been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's amendments of 07 September 2004 have overcome all rejections and objections not set forth below. Furthermore, the Examiner has found basis for unconserved transcriptionally active intergenic spacer regions on page 6 of the specification, lines 11-29.

The application should be reviewed for errors. Errors appear, for example, in claims 214, 217-218 and 220-223 as follows: In claim 214, line 6, "form" should be replaced with ---from---. Claims 217-218 and 220-221 are grammatically incorrect in their recitation of "control sequences...further comprises". Claim 222 incorrectly recites

"one of said...sequence", since claim 214 from which it depends claims more than one sequence, i.e. ---sequences---. In claim 223, line 2, "resistant" should be replaced with ---resistance---.

Claim 223 is objected to for encompassing non-elected subject matter, i.e. herbicide resistance genes. The Restriction requirement of 10 September 1999 indicated that herbicide resistance genes were assigned to either Group IX or Group X (see page 3 of that Office action). Applicant elected Group II, which excluded that subject matter, on page 7 of the Election of 27 January 2000. Claim 223 should be amended to remove the non-elected subject matter.

The allowability of claims 118-119 and 122, as indicated in the last Office action, is hereby WITHDRAWN in view of the new grounds of rejection under 35 USC 112, second paragraph.

Claims 118-119, 122, 214 and 223 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 118 is indefinite in its recitation of "wherein the peptide of interest is a biologically active molecule", which fails to further limit the claim, since claim 118 depends upon claim 107 which already recites this feature. Dependent claim 119 is included in the rejection.

Claim 122 is confusing in its dependency upon claim 188, which is drawn to biopolymer rather than a plant. Replacement of "188" with ---118---, if intended, would obviate this rejection.

Claim 214 remains indefinite in its recitation in lines 11-12 of "said homologous recombination" which lacks antecedent basis in the claim. Contrary to Applicant's arguments, the term "homologous recombination" does not appear in the amended claim prior to this recitation. Deletion of "said" before "homologous" in line 11 of the claim would obviate this rejection.

Claim 223 is indefinite in its recitation of "the herbicide resistance genes" which lacks antecedent basis. Deletion of "the" would obviate this rejection. However, as noted above, this is non-elected subject matter which should be deleted from the claim.

Claims 214 and 222-223 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 214 and dependents recite that an origin of replication is a type of 5' expression control sequence (see lines 6-7). However, there is no basis in the specification for this concept. Page 26 of the specification, lines 12-29, teach that an origin of replication is useful for promoting homoplasmy, but is different from a promoter or other type of 5' expression control region, because it has no effect on expression. Control regions affecting expression include promoters, as set forth on page 26, lines 33-36. Accordingly the recitation in claim 214 of "wherein the control sequence positioned upstream from [sic] the 5' end ... is an origin of replication" constitutes NEW MATTER.

Claims 3, 171, 190-191, 196, 214 and 216-223 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited to the intergenic spacer 2 region between the trnA and trnI genes of the chloroplast genome of higher plants, does not reasonably provide enablement for claims broadly drawn to the use of any transcriptionally active spacer region. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, as stated on pages 5-6 of the last Office action for claims 3, 171, 190-191, 196 and 214.

Claims 3, 171, 190-191, 193, 196, 214 and 216-223 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited to the intergenic spacer 2 region between the trnA and trnI genes of the chloroplast genome of higher plants for the homologous recombination-mediated insertion of heterologous DNA into the intergenic spacer 2 region of higher plants, does not reasonably provide enablement for the insertion of heterologous DNA into any "transcriptionally active" or "conserved" intergenic spacer region of the chloroplast genome of a multitude of higher plants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, as stated on page 6 of the last Office action for claims 190-191, 193, 196 and 214.

Applicant's arguments filed 28 June 2004 have been fully considered but they are not persuasive. Applicant urges that the enablement rejections are improper, given the ability of the skilled artisan to identify transcriptionally active regions by virtue of the

presence of a single promoter upstream of a polycistronic region, the existence of 60 such regions as demonstrated by Sugita et al cited previously, the ability of other workers to obtain success using other transcriptionally active regions, and the guidance in the specification regarding assays for finding other regions.

The Examiner maintains that Applicant states on page 7 of the specification that even among the genes of the ribosomal RNA (polycistronic) operon, there are few conserved regions (see, e.g., page 7 of the specification, lines 20-30). The use of unconserved regions would not result in homologous recombination into a variety of chloroplast genomes of a variety of plant species. See also page 8 of the specification, lines 23-34, which teach the importance of sequence conservation in the instant invention. Although Applicant has deleted reference to "conserved" regions from the claims, it appears that such conservation is crucial for the operability of the instant invention. The mere existence of transcriptionally active regions is insufficient, since unconserved regions would not be useful in homologous recombination with chloroplast genomes of unrelated plant species. Thus, the particularly exemplified transcriptionally active intergenic spacer 2 region appears to have the unique property of sequence conservation across divergent plant species, which property enables its use as a homologous recombination-mediated chloroplast transformation vector.

Regarding Sugita et al, the Examiner maintains that it is unclear whether the other regions in the operons taught by Sugita et al would be conserved among a variety of higher plant species. Regarding the results of other workers, as summarized on

pages 38-39 of the amendment of 28 June 2004, the references outlining such results were not submitted by Applicant, and so are not available for review by the Examiner.

Regarding the disclosure of assays in the specification, the Examiner maintains that such assays were only provided for identifying *conserved* transcriptionally active regions such as the exemplified intergenic spacer 2 region. Furthermore, the instant specification and the references previously cited by the Examiner demonstrate that the existence of other useful intergenic spacer regions, and their identification, is unpredictable.

It is also noted that an assay for *finding* a product is not equivalent to a positive recitation of *how to make* a product. Alternatively, disclosure of a method for producing a product does not reduce to practice the product itself. See *Bayer v. Housey*, Appeal No. 02-1598, (Fed. Cir. 2003), decided 22 August 2003, penultimate page: "processes of identification and generation of data are not steps in the manufacture of a final [drug] product".

Applicant is also directed to newly amended claims 214 and newly submitted claims 217-218 and 220-221 which merely recite the use of any origin of replication from any source, which origin of replication is supposed to be functional in a plant chloroplast in a plant cell. However, it is well-known that bacterial origins of replication will not function in plant cells. See page 26 of the specification, lines 12-29, which teach the requirement of a chloroplast origin of replication in the instant invention. See also claims 12-13 which specify a chloroplast origin of replication. Thus, newly amended

claim 214 and newly submitted claims 217-218 and 220-221 are not enabled by the specification.

Applicant is also directed to amended claims 191 and 196, which do not specify that the flanking DNA sequences are of chloroplast origin. Given the divergence of chloroplast versus nuclear DNA, as well as the divergence of plant versus animal or bacterial DNA, it is unlikely that non-chloroplast DNA can be used as flanking sequences to effect homologous recombination with portions of the chloroplast genome. Thus, claims 191 and 196 remain non-enabled for this aspect.

Applicant is also directed to claim 193, which specifies that the intergenic spacer 2 region may be used to insert the expression cassette into *any* region of the chloroplast DNA. Given the lack of sequence conservation among intergenic spacer regions, even within the ribosomal RNA operon, as stated above, claims drawn to the use of flanking regions which do not match the sequence of the target chloroplast genome are not enabled.

Claims 3, 171, 190-191, 193, 196, 214 and 216-223 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, as set forth on pages 9-10 of the last Office action for claims 3, 171, 190-191, 193, 196 and 214.

Applicant's arguments filed 28 June 2004 have been fully considered but they are not persuasive. Applicant urges that the specification provides examples of transformation of multiple plant species, and asserts that transcriptionally active spacer regions are conserved. The Examiner maintains that the specification admits that such regions are not in fact conserved, as stated on page 7 of the specification. Thus, Applicant has not identified any conserved sequences across the broad genus, which are correlated with the function of homologous recombination. Furthermore, Applicant's examples all involve the use of the single exemplified intergenic spacer 2 region. See the Written Description Guidelines cited previously.

Claims 3, 171, 190-191, 196, 214 and 216-223 are rejected under 35 U.S.C. 102(b) as being anticipated by Staub et al (1995), as stated on page 10 of the last Office action for claims 3, 171, 190-191 and 214.

Applicant's arguments filed 28 June 2004 have been fully considered but they are not persuasive. Applicant urges that the art rejection is improper, given the failure of the cited reference to teach integration into a conserved intergenic spacer region, the requirement that a 5' upstream promoter is required by the claimed invention, and the failure of the reference to teach insertion into a genomic region which is not transcriptionally silent.

The Examiner maintains that the claims have been previously amended to delete reference to sequence conservation. Furthermore, none of the rejected claims explicitly recites a promoter, and claim 214 implies that a promoterless construct is used, wherein homologous recombination results in the use of the native promoter on the chloroplast

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genome. It is also noted that the cited prior art teaches the use of the *rbcl* promoter, as stated previously. See page 845 of Staub et al, column 2, first paragraph under "Results".

Regarding the ultimate insertion of the expression cassette into a chloroplast genomic region, the Examiner notes that this is merely an intended use which is not given patentable weight in product claims. The claims themselves do not specify gene source, intergenic region source, or sequence of the flanking DNA sequences used in the expression and integration vector, and do not even specify that they are chloroplast DNA sequences. Furthermore, the specification states that the flanking sequences need not possess 100% sequence identity to the target chloroplast DNA genomic region, either along their entirety or even within small subsequences (see, e.g., page 26, top paragraph). Thus, the claims can be interpreted to encompass any expression vector containing any flanking regions which are of sufficient homology with a multitude of chloroplast regions, which regions are "not transcriptionally inactive", in order to effect homologous recombination therewith.

Claims 3, 171, 190-191, 196, 214 and 216-223 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-23, 25-29, 31 and 34 of U.S. Patent No. 5,923,479. Although the conflicting claims are not identical, they are not patentably distinct from each other because it would have been obvious to one of ordinary skill in the art to obtain the chloroplast expression vector comprising the promoter/structural gene/terminator flanked by chloroplast DNA for homologous recombination, and the resultant transformed plants,

as claimed in the instant application; by utilizing the chloroplasts transformed with an expression cassette comprising the same components as recited in the above expression vector, and the expression cassette and vector containing it, as claimed in the patent.

Applicant urges that the obviousness-type double patenting rejection is improper, given the recitation of at least two heterologous DNA sequences in the instant claims, and the failure of the patented claims to recite peptide-encoding sequences or multiple coding sequences or insertion into transcriptionally active chloroplast genomic regions.

The Examiner maintains that patent claims 23 and 29 recite that the chloroplast expression cassette comprises peptide-encoding genes. Furthermore, the open language of patent claim 19 indicates that the expression cassette may "comprise" more than one coding sequence. Thus, claims 22 and 28, reciting that the expression cassette also comprises a selectable marker gene, may be interpreted as "further comprising" said selectable marker gene. It is noted that instant claims 190 and 196 and dependents are only drawn to a single coding sequence and do not recite the presence of selectable marker genes. It is also noted that the instant claims do not specify the identity of the flanking DNA sequences, wherein the integration of the expression cassette into a particularly broadly claimed type of genomic region is merely an intended use not given patentable weight in product claims 190 and dependents. See also page 26 of the instant specification, top paragraph, which states that the flanking sequences need not have 100% sequence identity in order to function in the

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instant invention. Thus, given the amendment of the instant claims to delete "conserved" flanking regions, the claims are considered to be coextensive.

The rejected claims do not actually specify the identity or sequence of the flanking DNA regions. The claims merely indicate that insertion into the chloroplast genome occurs as "facilitated" by homologous recombination. Since non-chloroplast DNA regions are contemplated, as are any transcriptionally active intergenic spacer region, the claims could be interpreted to encompass any flanking sequence which possesses enough sequence homology to the claimed insertion points on the chloroplast genome. It is also noted that the claimed insertion points on the chloroplast genome are quite broad, namely anything which is not a transcriptionally inactive region.

Claims 3-84, 86-96, 107, 118-119, 122, 168-169, 172-176, 189 and 193-196 remain free of the prior art, as stated on page 11 of the last Office action.

Claims 4-84, 86-96, 107, 168-169, 172-176, 189 and 194-195 remain allowed, as stated on page 11 of the last Office action for claims 4-84, 86-96, 107, 118-119, 122, 168-169, 172-176, 189 and 193-196.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David T. Fox whose telephone number is (571) 272-0795. The examiner can normally be reached on Monday through Friday from 10:30AM to 7:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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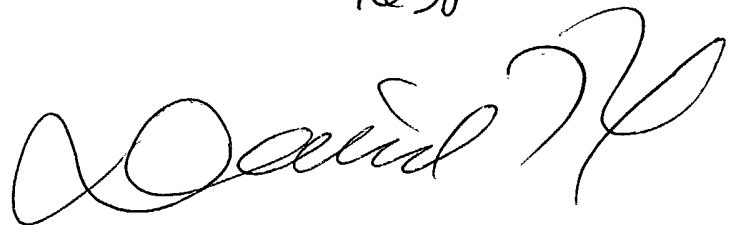
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November 12, 2004

DAVID T. FOX
PRIMARY EXAMINER
GROUP ~~180~~-1638

A handwritten signature in black ink, appearing to read "David T. Fox", written in a cursive style.